APPROVAL ORDER

00M-0580

AAV 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JAN - 7 2000

Mr. Ian R. McCue
McCue Corporation, Inc.
Harbor Towers, Apt. #729
5855 Midnight Pass Road
Sarasota, FL 34242

Re: P990016
McCue CUBAClinical Ultrasonic Bone Sonometry System with CUBA^{plus+} V4.2.0 Software
Filed: March 8, 1999
Amended: April 12, July 9 and 12, November 2, and December 3, 8, 13, and 22, 1999 and January 5, 2000.

Dear Mr. McCue:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the McCue CUBAClinical Ultrasonic Bone Sonometry System with CUBA^{plus+} V4.2.0 Software.

> The intended use of the McCue CUBAClinical Ultrasonic Bone Sonometry System is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid for the diagnosis of osteoporosis and other medical conditions leading to reduced bone density and, ultimately, for the determination of fracture risk.
>
> The CUBAClinical measures two parameters, Broadband Ultrasound Attenuation (BUA in dB/MHz) which is used for the clinical measurement and Velocity of Sound (VOS in m/s) which is used for QA purposes only. The BUA output is expressed both as an absolute value and, with reference to the embedded Normative Data, as a T-Score, Z-Score, and the percent expected (age-matched).

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520 (e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515 (d) (1) (B) (II0 of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch, (HFA-

305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when PMA applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at http://www.fda.gov/cdrh/pmat/pilotpmat.html for further details.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ewa Czerska at (301) 594-1212 x119.

Sincerely yours,

CAPT Daniel G. Schultz, M.D.
Acting Director
Division of Reproductive, Abdominal, Ear, Nose, and Throat, and Radiology Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1) May have caused or contributed to a death or serious injury; or

(2) Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc.

Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at 800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS INFORMATION

I. GENERAL INFORMATION

Device Generic Name(s):	Ultrasonic Bone Sonometer
Device Trade Name:	McCue CUBAClinical Ultrasonic Bone Sonometry System with CUBA*plus+* V4.1.0 Software
Applicant Name and Address:	McCue Corporation, Inc. Harbor Towers, Apt.729 5855 Midnight Pass Road Sarasota, FL 34242

Premarket Approval Application Number: P990016

Date of Panel Recommendation: N/A

Date of Notice of Approval to the Applicant: January 7, 2000

II. INDICATIONS FOR USE

The intended use of the McCue CUBAClinical Ultrasonic Bone Sonometry System is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid for the diagnosis of osteoporosis and other medical conditions leading to reduced bone density and, ultimately, for the determination of fracture risk.

The CUBAClinical measures two parameters, Broadband Ultrasound Attenuation (BUA in dB/MHz) which is used for the clinical measurement and Velocity of Sound (VOS in m/s) which is used for QA purposes only. The BUA output is expressed both as an absolute value and, with reference to the embedded Normative Data, as a T-Score, Z-Score, and the percent expected (age-matched).

III. CONTRAINDICATIONS

There are no known contraindications associated with the use of the McCue CUBAClinical system.

IV. WARNINGS AND PRECAUTIONS

See labeling for warnings and precautions.

V. DEVICE DESCRIPTION

The McCue CUBAClinical Ultrasonic Bone Sonometry System performs quantitative ultrasound measurement of the calcaneus by passing non-audible, high frequency sound waves through the heel. The System is small, lightweight (10 Kg), and portable. It plugs into a standard power outlet. Ultrasound measurements are performed with the patient seated, and the foot positioned and secured. Use of Foot Positioning Inserts is determined by patient foot size.

After the patient's foot is secured, using Velcro® straps, and coupling gel is applied, a pair of silicone elastomer covered transducer heads is brought into contact with opposite sides of the patient's heel. One transducer transmits the sound wave and the other, on the opposite side of the patient's heel, receives the sound wave. The results are then analyzed and displayed on the screen of the computer. The ultrasound power levels used by the CUBAClinical are lower than the limits for standard imaging ultrasound devices set forth in the 1997 FDA Guidance Document, "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers".

A. System Components

The McCue CUBAClinical Ultrasonic Bone Sonometry System consists of the following components: CUBAClinical Unit with carrying case, the serial cable, the power cable, the hybrid phantom for routine quality assurance testing (in its own carrying case), the User Manual, a set of Foot Positioning Inserts, the CUBA*plus+* V4.1.0 software on one 3.5" diskette (1.44 MB diskette), and ultrasound coupling gel. Additional equipment

necessary for operation includes a user-supplied desktop or portable computer (PC) with display and printer.

B. System Operation

The McCue CUBAClinical is controlled by push buttons on the unit and by a user-supplied PC. Operator instructions and results are displayed on the screen of the PC. A hard copy printout of measurement results can be obtained using the user-supplied printer. The printout reports the subject's BUA, T-Score, Z-Score, and as a percentage expected (age matched) (%exp). In addition, the printout displays the subject's results graphically. Additional information entered in the patient record is the patient identification information and demographic information (age, sex, etc.).

For measurement, the operator applies ultrasound coupling gel to the subject's heel. The subject then places the designated foot into the footwell. Labels inside the footwell indicate if and which size Foot Positioning Insert should be used. Once the foot is positioned, the operator secures the calf into position with the Velcro® straps and activates the transducers by pushing a button. Following a settling period of 30 seconds, the CUBAClinical takes a minimum of three separate readings of BUA and providing that they are within a defined tolerance, the mean value is calculated and reported as the result. Results are displayed on the PC screen, retained on hard disk, and are available for printing.

The McCue CUBAClinical is provided non-sterile and is not intended to be sterilized. The User Manual provides instructions for post-use decontamination. The System is indicated for use with intact skin only. Low level disinfection using hospital-grade solutions is recommended.

C. Principles of Operation

For ultrasonic measurements of the calcaneus, the CUBAClinical uses two ultrasound transducers: one as the transmitter, and one as the receiver. The measurement provided by the CUBAClinical, broadband ultrasound attenuation (BUA) is defined as the slope (dB/MHz) between attenuation (dB) and frequency, typically between 0.2 MHz and 0.6 MHz.

VOS (velocity of sound, in m/s) is used in the QA test with the Phantom. For calculation of VOS, a linear transducer measures the distance between the two-ultrasound transducers. Transit time is calculated from the point source of the ultrasound signal to the leading edge of its detection with adjustment for the transit time through the transducer face- plates and the silicone pads.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Traditional methods for assessing bone quality use x-rays to estimate bone mineral density (BMD) and expose the patient and operator to ionizing radiation. These methodologies include single energy X-ray absorptiometry (SXA), dual energy X-ray absorptiometry (DEXA or DXA), quantitative computed tomography (QCT), single photon absorptiometry (SPA), and dual photon absorptiometry (DPA). Of these techniques, SXA, DXA, and SPA have been used specifically for the estimation of BMD of the calcaneus.

Of the traditional X-ray based methods for assessing bone density, the dual energy X-ray absorptiometry (DXA) and single energy X-ray absorptiometry (SXA) techniques are the most widely used. These established techniques estimate BMD at a variety of anatomical sites, including the heel, by measuring the attenuation of X-rays due to passing through the bone.

FDA has recently approved several quantitative ultrasound devices, which measure BUA and VOS for the assessment of bone quality for osteoporosis and determination of fracture risk.

VII. MARKETING HISTORY

CUBAClinical Systems have been sold in 21 countries, including the United Kingdom, Ireland, Australia, Argentina, Japan, Korea, Taiwan, Singapore, New Zealand, Italy, Spain, Switzerland, Holland, Sweden, Greece, Turkey, the Czech Republic, Iceland, Hong Kong, Syria, and Austria. No McCue CUBAClinical System has been withdrawn from the market for any reason related to safety and effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS ON HEALTH

There are no known potential adverse effects of this device on health. The McCue CUBAClinical uses ultrasound power levels lower than standard ultrasound

imaging devices, which are widely used and accepted. No adverse events of any kind have been reported.

IX. SUMMARY OF NON-CLINICAL STUDIES

The McCue CUBAClinical is a non-critical, reusable medical device with contact to intact patient skin for approximately two minutes per measurement. Areas of patient risk associated with system operation were evaluated in non-clinical studies.

A. Electrical Safety

The CUBAClinical is in compliance with EN60601-1 Medical Electrical Equipment: General Requirements for Safety.

B. Electromagnetic Compatibility

The CUBAClinical complies with IEC 60601-1-2 (1993) and FCC Part 15 Subpart B, Class A (1996) for electromagnetic compatibility.

C. Software

Software verification tests used for the CUBAClinical were submitted by McCue PLC. A hazards analysis indicated that all software and hardware patient and user concerns were adequately addressed. Verification, validation, and unit testing demonstrate that the device operates in a manner described in the System Specification.

D. Acoustic Output

McCue PLC provided testing to demonstrate the acoustic output of the CUBAClinical transducers. Intensities are within the limits specified in CDRH Guidance, "Information for Manufacturers seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" (1997). Global Maximum Value of MI (mechanical index) = 0.27(±17%), I_{spta3} =5.3(±31%) μW/cm^2, and I_{sppa3} = 1.9(±32%) W/cm^2.

E. Biological/Sterility

The materials used for silicone pads covering the ends of the transducers are medical grade silicones for which FDA has Master Files. McCue PLC has submitted authorization from the manufacturer to reference these files.

The material for the Calf Plate Support and Foot Positioning Inserts, acrylic-capped ABS plastic, was tested for toxicity (in vitro and in vivo). The in vivo sensitization study of the material used for the CUBAClinical case and external parts (acrylic capped ABS plastic) suggests that this material may be a potential sensitizer. The CUBAClinical is intended for use in patients with intact skin and without evidence of skin irritation. The acute cutaneous irritation test, which most closely replicates clinical conditions of use, showed no evidence of irritation after four hours of exposure over freshly shaved skin.

F. Evaluation of Design Variation

To demonstrate that the CUBAClinical intended for marketing in the U.S. is equivalent to the design that was used for the collection of clinical data, a side-by-side comparison was conducted using the Hybrid Phantom. The coefficient of variation (CV%) for the proposed device was 0.626 for BUA and 0.2458 for VOS. CV% specifications for BUA and VOS are 1% and 0.5% respectively. The CV% values for BUA and VOS for the previous model were 1.7467 and 0.1836 respectively.

X. SUMMARY OF CLINICAL STUDIES

A. Introduction

Clinical studies of the McCue CUBAClinical were submitted in support of the PMA to:

(1) support the safety, effectiveness, and clinical utility of the McCue CUBAClinical. Results from five studies performed at six international clinical sites involving 1343 subjects were provided to demonstrate that the CUBAClinical is safe, to compare CUBAClinical BUA results to bone mineral density results obtained at the calcaneus, femoral neck, and spine,

and to assess the ability of the CUBAClinical BUA to predict risk of osteoporotic fractures in the elderly.

(2) demonstrate the precision of the CUBAClinical

(3) describe the reference population used by the CUBAClinical

(4) demonstrate that the performance of the proposed device model is equivalent to that of the model used in the clinical studies

B. Safety, Effectiveness, and Clinical Utility

Five studies performed at six sites in the U.S. and Europe were used to support the safety, effectiveness, and clinical utility of the McCue CUBAClinical.

Table 1. Summary of Clinical Studies

Clinical Center	Investigators	Number of Evaluable Subjects	Study Designation
Beth Israel Deaconess Medical Center Boston, Massachusetts	S. L. Greenspan M.L. Bouxsein	159 females	Study A
Oregon Health Sciences University Portland, Oregon	K. G. Faulkner E. S. Orwoll		
Vrije Unviersiteit, Amsterdam, Netherlands	S. M. F. Pluijm W. C. Graafmans L. M. Bouter P. Lips	583 females 132 males	Study B
Centre for Metabolic Bone Disease Hull Royal Infirmary, Hull, UK	C. M. Langton	105 females	Study C
University of Aberdeen, UK	D. M. Reid A. Stewart	246 females	Study D
		118 females	Study E

Objectives of the studies included an assessment of the performance of the CUBAClinical, and a comparison of its performance to bone mineral densitometry systems. The studies were designed to assess the following:

(1) the relationship of CUBAClinical BUA to specific patient characteristics, such as age and sex;

(2) use of CUBAClinical BUA for predicting fracture risk;

(3) the ability of CUBAClinical BUA to discriminate osteoporotic subjects from non-osteoporotic subjects, and subjects with fractures from non-fracture subjects;
(4) the correlation of CUBAClinical BUA with results obtained using other ultrasound techniques; and
(5) the correlation of CUBAClinical BUA results with results obtained using radiological methods.

STUDY A: Fosamax Protocol 349

This study was conducted at two clinical sites in the United States to determine if measuring skeletal status at the calcaneus is a useful technique for diagnosis of osteoporosis. It was designed to evaluate precision, correlation, and discrimination ability of five calcaneal bone assessment instruments. The study enrolled a total of
161 Caucasian women: 53 were "young normal" women between the ages of 20 and 35 (mean age: 30.2); and 52 were osteoporotic women with no history of fracture; and 56 were osteoporotic women without a history of fracture. The 108 osteoporotic women were all between the age of 55 and 92 (mean age: 72.5). Subjects were considered to be osteoporotic if they had a femoral neck or trochanter BMD T-Score of -2.5 or lower. CUBAClinical BUA measurements were performed on the subjects using the CUBAClinical as well as DEXA and SEXA of the calcaneus, hip, and spine. In addition, measurements were performed using three other calcaneal ultrasound devices, but these devices were not included in the analysis presented in the PMA. Complete results for all devices tested are provided in a report published by Greenspan, et al (1997).

Femoral neck and trochanter BMD T-Scores using device-specific reference populations were used to qualify subjects for enrollment in the osteoporotic cohorts. T-Scores for all instruments for all other analyses were determined using the young normal subjects, thereby providing a common reference population.

Pearson's product moment correlation coefficients were determined for age and CUBAClinical BUA measurements and for the DEXA and SEXA devices. For all study subjects, the correlation between subject age and the instrument measurements ranged from -0.677 (BMD calcaneus) to -0.836 (BMD femoral neck). The correlation coefficient for CUBAClinical BUA was approximately in the middle of this range at -0.743.

The correlation of the CUBAClinical BUA T-Scores to the T-Scores for the BMD measurements was determined. Pearson's correlation coefficients for BUA versus each of the DEXA and SEXA devices ranged from 0.696 (BUA versus DEXA of the trochanter) to 0.821 (BUA versus DEXA of the calcaneus). Correlations among the different BMD measurements ranged from 0.729 (DEXA calcaneus versus DEXA femoral neck) to 0.908 (DEXA calcaneus versus SEXA calcaneus).

T-Scores for fracture and non-fracture cohorts for CUBAClinical BUA measurements, DEXA measurements, and SEXA measurements at different anatomical sites are given in Table 2. For all of the devices studied, the mean T-Scores for the fracture groups were significantly lower than the mean T-Scores for the non-fracture groups ($p<02$). Duncan's Multiple Range Test was used to compare the mean T-Scores for the CUBAClinical BUA and the SEXA and DEXA measurements for all osteoporotic subjects. This test found that the mean T-Score for CUBAClinical BUA was not significantly different from the mean BMD T-Scores for DEXA calcaneus and DEXA trochanter. BMD T-Scores for DEXA femoral neck and SEXA calcaneus were also not significantly different.

Table 2. Summary of T-Scores for Study A Osteoporotic Subjects

		Osteoporotic		
Instrument		No Fracture (n=49)	Fracture (n=55)	All (n=104)
CUBAClinical BUA	Mean	-1.77	-2.24	-2.02
	SD	0.837	0.859	0.877
OsteoAnalyzer (BMC)	Mean	-1.99	-2.62	-2.32
(SEXA calcaneus)	SD	1.015	1.186	1.148
QDR-1500/2000 (BMD)	Mean	-1.76	-2.305	-2.05
(DEXA calcaneus)	SD	1.141	1.219	1.208
QDR-1500/2000 (BMD)	Mean	-1.71	-2.13	-1.93
(DEXA trochanter)	SD	0.698	0.810	0.783
QDR-1500/2000 (BMD)	Mean	-2.30	-2.54	-2.43
(DEXA femoral neck)	SD	0.413	0.592	0.527

The ability of CUBAClinical BUA, DEXA calcaneus BMD, and SEXA calcaneus BMD to discriminate between osteoporotic and non-osteoporotic controls was assessed for T-Score thresholds of -2.5 and -2.0. For a T-Score threshold of -2.5, the proportion of subjects classified as osteoporotic by CUBAClinical BUA was 31 percent. This compares to 39 percent and 47 percent for DEXA calcaneus and

SEXA calcaneus, respectively. For a T-Score threshold of -2.0, the number of subjects correctly classified as osteoporotic ranged from 53 to 69 percent, with CUBAClinical BUA at 58 percent.

Receiver-Operator Characteristic (ROC) curves were generated to determine the ability of CUBAClinical BUA and DEXA and SEXA of the calcaneus to discriminate osteoporotic subjects from the young normal control group. In addition, ROCs and the areas under the ROC curves were generated to discriminate between osteoporotic subjects with fractures from those without fractures. The area under an ROC curve provides a figure of merit for comparing one curve to another. The AUC must be greater than 0.5 if the diagnostic ability is better than chance. A summary of the AUCs obtained for the three instruments is provided in Table 3.

Table 3. Areas Under the ROC Curves for Study A

Instrument	Control vs Osteoporotic AUC (95%CI)	Osteoporotic w/o vs Osteoporotic w/fracture AUC (95%CI)
CUBAClinical BUA	0.93 (0.89, 0.97)	0.63 (0.53, 0.73)
OsteoAnalyzer (SEXA calcaneus)	0.93 (0.89, 0.97)	0.65 (0.55, 0.75)
QDR 1500/2000 (DEXA calcaneus)	0.90 (0.86, 0.94)	0.62 (0.52, 0.72)
QDR 1500/2000 (DEXA trochanter)	0.93 (0.89, 0.97)	0.65 (0.52, 0.75)
QDR 1500/2000 (DEXA femoral neck)	0.98 (0.96, 1.00)	0.60 (0.48, 0.72)

To further compare the discriminatory ability of CUBAClinical BUA to the X-ray absorptiometry instruments, the sensitivity and specificity of each instrument was determined for T-Score thresholds of -1.5, -2.0, and -2.5. The results, summarized in Table 4, indicate that the sensitivity and specificity of CUBAClinical BUA is comparable to that of SEXA of the calcaneus and DEXA of the calcaneus.

Table 4. Comparison of Sensitivity and Specificity of Calcaneal Instruments in Study A

Instrument	T-Score Threshold	Sensitivity (%)	Specificity (%)
CUBAClinical BUA	-1.5	77 %	96 %
	-2.0	58 %	96 %
	-2.5	31 %	100 %
QDR-1500/2000 (DEXA calcaneus)	-1.5	69 %	92 %
	-2.0	54 %	98 %
	-2.5	36 %	98 %
OsteoAnalyzer (SEXA calcaneus)	-1.5	77 %	94 %
	-2.0	67 %	96 %
	-2.5	44 %	100 %

STUDY B: Netherlands Study of Fracture Risk

This prospective longitudinal study was conducted to determine the possible contribution of CUBAClinical BUA for assessing risk of osteoporotic fracture in the elderly. The study was conducted at the Institute of Research in Extramural Medicine Academic Hospital, Vrije University, Amsterdam, Netherlands. Dr. S.M.F. Pluijm was the Principle Investigator. A total of 710 Caucasian subjects between the ages of 70 and 99 were enrolled in the study, of whom 578 were women and 132 were men. Subjects were excluded if they were unable to give informed consent, had a history of calcaneal fracture, were confined to bed, or used a wheelchair.

CUBAClinical measurements were performed at time of enrollment. Subjects were contacted every six months by telephone or self-administered mail questionnaire to determine if they had a fall or fracture during the previous month. Fractures were verified with the subject's primary physician. During the time of the study, 168 subjects died and 5 were lost to follow-up. The study accumulated 1844 person-years of follow-up (median: 2.8 years, maximum: 3.7 years).

During the period of follow-up, 77 of the subjects (73 females and 4 males) sustained a total of 96 fractures (31 hip and 65 other non-spinal fractures). Table 5 compares the baseline CUBAClinical BUA measurement for the 77 subjects with fractures and the subjects without fractures. The differences in BUA between the females with and without fracture were statistically significant.

Table 5. Summary of Baseline CUBAClinical BUA Measurements by Fracture Status and Sex for Study B

	CUBAClinical BUA (dB/MHz) (Mean (SD))		
	Fracture	Non Fracture	p value*
Female Mean (SD)	n=73 51.27 (15.88)	n=503 56.92 (17.52)	0.010
Male Mean (SD)	n=4 66.81 (16.56)	n=128 81.05 (21.57)	0.194
Combined Mean (SD)	n=77 52.08 (16.18)	n=631 61.81 (20.80)	<0.001

Significance level for paired t-test comparing mean for fracture versus non-fracture subjects.

Relative hazard ratios were determined using Cox proportional hazard regression and are reported here with 95 percent confidence intervals. The relative hazard ratio of hip fracture, other non-spinal fractures, and any non-spinal fractures for one standard deviation decrease in CUBAClinical BUA is summarized by subject sex and for all subjects in Table 6 below. An increased relative hazard ratio is indicated by values greater than 1.0. As shown in Table 6, the relative hazard ratio for CUBAClinical BUA is greater than 1.0 for hip fractures and any non-spinal fractures in female subjects. The lower 95% CI is less than 1.0 for other non-spinal fractures, and for all non-spinal fracture endpoints in the male population.

Table 6. Relative Hazard Ratio of Hip, Other Non-Spinal, and Any Non-Spinal Fracture for CUBAClinical BUA for Study B

Gender		Hip Fracture		Other Non-Spinal Fractures		Any Non-Spinal Fracture	
		RR	95%CI	RR	95%CI	RR	95%CI
Females	BUA	2.27	1.41-3.66	1.29	0.96 – 1.73	1.52	1.17 - 1.97
Males	BUA	2.68	0.79 - 9.06	2.71	0.24 - 30.71	2.68	0.79 - 9.06
Overall	BUA	2.34	1.46 - 3.75	1.62	1.18 – 2.22	1.83	1.39 - 2.42

STUDY C: Centre for Metabolic Bone Disease, Hull Royal Infirmary, Hull, U.K.

This study was conducted by Christian M. Langton, Ph.D. to assess the usefulness of the McCue CUBAClinical to pre-screen subjects for bone density measurements and to determine if assessment with the CUBAClinical was superior to presently used clinical referral criteria. Data collected in this study were analyzed to assess the diagnostic performance of the CUBAClinical and how its performance compares to DEXA BMD.

This was an open enrollment study of 106 Caucasian female subjects between the age of 60 and 69 (mean: 64 years) who were recruited from the general patient population of three local general practitioners. Subjects were excluded if they weighed more than 280 pounds, had bilateral foot deformity, and were participating in a research study for another medical device or drug. One subject was excluded from analysis, leaving a total of 105 subjects.

BMD measurements of the spine and femoral neck and CUBAClinical BUA measurements were performed on all subjects on the same day. BUA measurements were performed on both heels of all subjects. Analysis of the results found that differences in the mean BUA for the right and left heel was not significantly different. Therefore, the left heel results were used in the analysis for all subjects.

Subjects were also evaluated to determine if they met one or more of five clinical referral criteria used for referring subjects to BMD. Forty-seven of the 105 subjects (45 percent) met one or more of the five general clinical referral criteria for BMD. The age, height, weight, CUBAClinical BUA measurements, spinal BMD and femoral neck BMD values of the 47 subjects meeting at least one of the clinical referral criteria was compared to that of the other 58 subjects who did not meet any of the clinical referral criteria. Differences in these parameters between the two groups were not statistically significant.

The ability of CUBAClinical BUA to identify subjects that BMD classifies as normal, osteopenic, or osteoporotic was assessed. Each subject was classified as normal, osteopenic, or osteoporotic based on the values for BMD spine and BMD femoral neck given in the operating instructions for the Lunar DPX-1. Table 7 summarizes these classifications.

Table 7. Classification of Study C Subjects Based on Femoral Neck BMD and Spine BMD

Diagnostic Category	Number of Subjects Classified by Femoral Neck BMD	Number of Subjects Classified by Spine BMD
Normal	34 (32%)	49 (47%)
Osteopenic	58 (55%)	36 (34%)
Osteoporotic	13 (12%)	20 (19%)
Total	105 (100%)	105 (100%)

Thirteen of the 105 subjects were classified as osteoporotic by femoral neck BMD, and 20 subjects were classified as osteoporotic by spine BMD. Clinical referral criteria was positive on 4 of the 13 (31%) osteoporotics identified by femoral neck BMD, and 9 of the 20 osteoporotics (45 %) identified by spine BMD.

Table 8 summarizes the CUBAClinical BUA T-Scores and Z-Scores for the three diagnostic classifications as assigned by femoral neck BMD, and Table 9 summarizes the CUBAClinical BUA T-Scores and Z-Scores for the diagnostic classifications assigned by spine BMD. In both tables, mean T-Scores and Z-Scores get progressively lower from the normal group to the osteoporotic group. The osteoporotic groups had mean BUA T-Scores of -2.15 regardless of whether femoral neck or spine BMD was used to classify subjects. The mean Z-Scores of the osteoporotics were also virtually identical (-0.67 and -0.69) for either classification.

Table 8. Summary of Study C CUBAClinical BUA T-Scores and BUA Z-Scores by Diagnostic Group as defined by Femoral Neck BMD [Means (SD)]

Groups defined by Femoral Neck BMD	CUBAClinical BUA T-Score	CUBAClinical BUA Z-Score
Normal (n=34; 33%)	-0.88 (0.91)	0.56 (0.91)
Osteopenic (n=58; 55%)	-1.50 (0.75)	-0.03 (0.75)
Osteoporotic (n=13; 12%)	-2.15 (1.13)	-0.67 (1.09)

Table 9. Summary of Study C CUBAClinical BUA T-Scores and BUA Z-Scores by Diagnostic Group as defined by Spine BMD [Mean (SD)]

Groups defined by Spine BMD	CUBAClinical BUA T-Score	CUBAClinical BUA Z-Score
Normal (n=49; 47%)	-1.05 (0.83)	0.40(0.82)
Osteopenic (n=36; 34%)	-1.40 (0.91)	0.07 (0.91)
Osteoporotic (n=20; 19%)	-2.15 (0.78)	-0.69 (0.75)

ROC curves were generated for CUBAClinical BUA, femoral neck BMD, and spine BMD, and areas under the ROC curves were determined. The areas under the curves are summarized in Table 10.

Table 10. Areas under the ROC Curves for Discrimination of Osteoporotic from Non-Osteoporotic Subjects as defined by BMD (Femoral Neck and Spine) for Study C

Measurement	Osteoporosis Defined by Femoral Neck BMD AUC (95% CI)	Osteoporosis Defined by Spine BMD AUC (95% CI)
CUBAClinical BUA	0.72 (0.56, 0.88)	0.79 (0.67, 0.91)
BMDFemoral Neck		0.87 (0.77, 0.97)
BMD Spine	0.89 (0.77, 1.01)	

Sensitivity and specificity for CUBAClinical BUA discrimination of osteoporotic subjects from non-osteoporotic subjects were determined for T-Score thresholds of -2.5, -2.0, and -1.5. Classification of each subject as osteoporotic was based on the femoral neck or spine BMD values, as summarized in Tables 8 and 9 above. Table 11 summarizes the sensitivity and specificity of BUA based on femoral neck or spine BMD classifications. It also shows the number of subjects that were classified as osteoporotic by both BUA and BMD. At a T-Score of -2.0, CUBAClinical BUA has a sensitivity of about 60 percent, and a specificity of about 80 percent. For comparison, the sensitivity and specificity of clinical referral criteria was 31 percent and 53 percent, respectively, for osteoporosis as defined by femoral neck BMD, and 45 percent and 55 percent, respectively, for osteoporosis as defined by spine BMD.

Table 11. Summary of CUBAClinical BUA Sensitivity and Specificity for Study C

CUBAClinical BUA T-Score Thresholds		Osteoporotic by Femoral Neck BMD (n=13)	Osteoporotic by Spine BMD (n=20)
-2.5	Number (%) Identified by BUA as osteoporotic	5 (38 %)	6(30 %)
	Sensitivity	38 %	30 %
	Specificity	91 %	92 %
-2.0	Number (%) Identified by BUA as osteoporotic	8 (62 %)	12(60 %)
	Sensitivity	62 %	60 %
	Specificity	80 %	82 %
-1.5	Number (%) Identified by BUA as osteoporotic	8 (62 %)	15 (75 %)
	Sensitivity	62 %	75 %
	Specificity	60 %	65 %

STUDY D: University of Aberdeen

This study was conducted at the Osteoporosis Research Unit at the University of Aberdeen, Foresterhill, U.K., by Doctors David M. Reid and Alison Stewart. A total of 250 Caucasian women who had no history of osteoporotic fracture and who were referred for bone mineral density scans were enrolled in the study. Four subjects were missing critical data, and were excluded from the analysis. The age of the subjects ranged from 23 to 79 (mean 54), and 184 (75 percent) were post-menopausal.

BMD of the hip and spine and CUBAClinical BUA were measured on each subject on the same day. T-Scores for the CUBAClinical BUA were calculated using the machine reference population. T-Scores for BMD were determined using a site-specific local reference population. Table 12 summarizes the mean T-Scores and Z-Scores for the CUBAClinical BUA and BMD measurements.

Table 12. Summary of T-Scores and Z-Scores for Study D

Instrument	T-Score Mean (SD)	Z-Score Mean (SD)
CUBAClinical BUA	-1.36 (1.02)	0.14 (0.95)
Femoral Neck BMD	-1.29 (1.15)	-0.23 (0.98)
Spine BMD	-1.69 (1.44)	-0.21 (1.03)

Pearson's product moment correlation coefficients were generated for the CUBAClinical BUA, BMD femoral neck, and BMD spine measurements. CUBAClinical and the BMD measurements exhibited moderate correlations. The highest correlation (0.774) was found for femoral neck BMD to spine BMD. Other correlations ranged from 0.450 to 0.662.

Subjects were categorized as osteoporotic, osteopenic, or normal according to the BMD T-Scores of the femoral neck and spine using established WHO criteria. Thirty-one subjects were classified as osteoporotic by femoral neck BMD, and 73 were classified as osteoporotic by spine BMD. The ability of CUBAClinical BUA to discriminate between osteoporotic and non-osteoporotic subjects was evaluated using BUA T-Score thresholds of -2.5, -2.0, and -1.5. Table 13 summarizes the CUBAClinical BUA T-Scores and Z-Scores for the diagnostic classifications assigned by femoral neck BMD. Also shown, for comparison, are the spine BMD T-Scores and Z-Scores for the femoral neck BMD classifications. Likewise, Table 14 summarizes the T-Scores and Z-Scores for the diagnostic classifications assigned by spine BMD. In both tables, mean T-Scores and Z-Scores get progressively lower from the normal group to the osteoporotic group.

Table 13. CUBAClinical BUA T-Scores and Z-Scores for Diagnostic Categories Defined by Femoral Neck BMD [Mean (SD)] for Study D

Diagnostic Category as Defined by Femoral Neck BMD T-Scores (Number of Subjects; %)	CUBAClinical BUA		BMD Spine	
	T-Score	Z-Score	T-Score	Z-Score
Normal (n=98; 40%)	-0.85 (0.95)	0.45 (0.93)	-0.67 (1.32)	0.32 (1.07)
Osteopenic (n=117; 48%)	-1.53 (0.82)	0.04 (0.87)	-2.12 (0.97)	-0.46 (0.82)
Osteoporotic (n=31; 12%)	-2.37 (0.94)	-0.46 (0.96)	-3.26 (0.97)	-1.05 (0.75)

Table 14. CUBAClinical BUA T-Scores and Z-Scores for Diagnostic Categories

Defined by Spine BMD [Mean (SD)] for Study D

Diagnostic Category as Defined by Spine BMD T-Scores (Number of Subjects; %)	CUBAClinical BUA		BMD Femoral Neck	
	T-Score	Z-score	T-Score	Z-score
Normal (n=72; 29%)	-0.78 (0.92)	0.54 (0.88)	0.20 (0.94)	0.56 (0.97)
Osteopenic (n=101; 41%)	-1.35 (0.87)	0.10 (0.92)	-1.40 (0.77)	-0.36 (0.74)
Osteoporotic (n=73; 30%)	-1.96 (0.95)	-0.19 (0.91)	-2.20 (0.86)	-0.83 (0.74)

ROC curves were generated to evaluate the ability of CUBAClinical BUA to discriminate between osteoporotic and non-osteoporotic subjects as classified by femoral neck BMD and spine BMD T-Scores. The areas under the ROC curves with 95 percent confidence intervals are provided in Table 15.

Table 15. Areas under the ROC Curves for Discrimination of Osteoporotic from Non-Osteoporotic Subjects as defined by BMD (Femoral Neck and Spine) for Study D

Measurement Technique	Osteoporosis Defined by Femoral Neck BMD AUC (95% CI)	Osteoporosis Defined by Spine BMD AUC (95% CI)
CUBAClinical BUA	0.73 (0.63, 0.83)	0.73 (0.67, 0.79)
BMD Femoral Neck		0.83 (0.77, 0.89)
BMD Spine	0.85 (0.80, 0.94)	

Sensitivity and specificity for CUBAClinical BUA discrimination of osteoporotic subjects from non-osteoporotic subjects were determined for T-Score thresholds of -2.5, -2.0, and -1.5. Classification of each subject as osteoporotic was based on femoral neck or spine BMD T-Scores of -2.5 or less. Table 16 summarizes the sensitivity and specificity of BUA based on the resulting femoral neck or spine BMD classifications. It also shows the number of subjects that were classified as osteoporotic by both BUA and BMD. At a T-Score of -2.0, CUBAClinical BUA has a sensitivity of 61 percent, and a specificity of 81 percent when osteoporosis is defined by femoral neck BMD. When osteoporosis is defined by spine BMD, BUA has a sensitivity of 49 percent and a specificity of 87 percent.

Table 16. Summary of Sensitivity and Specificity for CUBAClinical BUA for Study D

CUBAClinical BUA T-Score Thresholds		Osteoporotic by Femoral Neck BMD (n=31)	Osteoporotic by Spine BMD (n=73)
-2.5	Number (%) Identified	13 (42 %)	18 (25 %)
	Sensitivity	42 %	25 %
	Specificity	92 %	93 %
-2.0	Number (%) Identified	19 (61 %)	36 (49 %)
	Sensitivity	61 %	49 %
	Specificity	81 %	87 %
-1.5	Number (%) Identified	25 (81 %)	49(68 %)
	Sensitivity	81 %	68 %
	Specificity	59 %	63 %

STUDY E: University of Aberdeen

This study was also conducted at the Osteoporosis Research Unit, University of Aberdeen. The principle Investigator was Dr. Alison Stewart. This was an open enrollment study for Caucasian women who were referred to the Osteoporosis Research Unit for a DEXA scan of the spine and hip. Subjects were evaluated with two ultrasound devices, the CUBAClinical and the Lunar Achilles, and had BMD of the hip, spine, and heel measured. All measurements were performed on the same day.

A total of 138 Caucasian women subjects were enrolled. Twenty of the 138 subjects were missing a key measurement and were excluded from this analysis. The subjects ranged in age from 33 to 80 years (mean: 56 years), but 82 percent of the subjects were between the ages of 50 to 59. Ninety-six subjects (82 percent) were post-menopausal. Table 17 summarizes the T-Scores and Z-Scores for CUBAClinical BUA, Lunar Achilles Stiffness Index, and BMD of the femoral neck, spine, and heel.

Table 17. Summary of T-Scores and Z-Scores [Mean (SD)] for Study E

Device/Measurement	T-Score	Z-Score
CUBAClinical BUA	-1.50 (0.90)	-0.32 (0.85)
Lunar Achilles Stiffness	-1.65 (1.18)	-0.17 (1.09)
Femoral Neck BMD	-0.98 (1.01)	-0.43 (0.89)
Spine BMD	-1.30 (1.47)	0.10 (1.14)
Heel BMD	-0.12 (1.15)	not available

Pearson's product moment correlation coefficients were generated for CUBAClinical BUA, Lunar Achilles Stiffness Index, BMD femoral neck, BMD spine, and BMD heel measurements. CUBAClinical and the BMD measurements exhibited moderate correlations. The highest correlation was between CUBAClinical BUA and the Achilles Stiffness Index (0.801). Correlations between CUBAClinical and BMD measurements were moderate, ranging from 0.420 to 0.646 and were comparable to the correlations between the different BMD sites (.570 to .655), and the correlations between the Achilles Stiffness Index and BMD (0.575 to 0.762).

Subjects were categorized as osteoporotic, osteopenic, or normal according to the BMD T-Scores of the femoral neck and spine using established WHO criteria. Eleven subjects were classified as osteoporotic by femoral neck BMD, and 24 were classified as osteoporotic by spine BMD. The ability of CUBAClinical BUA to discriminate between the osteoporotic and non-osteoporotic subjects was evaluated using BUA T-Score thresholds of -2.5, -2.0, and -1.5. Table 18 summarizes the CUBAClinical BUA T-Scores and Z-Scores for the diagnostic classifications assigned by femoral neck BMD. Also shown, for comparison, are the spine BMD T-Scores and Z-Scores for the femoral neck BMD classifications. Likewise, Table 19 summarizes the CUBAClinical BUA T-Scores and Z-Scores for the diagnostic classifications assigned by spine BMD. In both tables, mean T-Scores and Z-Scores get progressively lower from the normal group to the osteoporotic group.

Table 18. CUBAClinical BUA T-Scores and Z-Scores for Diagnostic Categories Defined by Femoral Neck BMD [Mean (SD)] for Study E

Diagnostic Class as Defined by Femoral Neck BMD T-Scores (# Subjects; %)	CUBAClinical BUA		Spine BMD	
	T-Score	Z-Score	T-Score	Z-Score
Normal (n=79; 67%)	-1.30 (0.79)	-0.16 (0.79)	-0.98 (1.27)	0.23 (1.11)
Osteopenic (n=28; 24%	-1.66(0.92)	-0.48 (0.91)	-1.55 (1.45)	-0.09 (1.16)
Osteoporotic (n=11; 9%)	-2.60 (0.78)	-1.08 (0.66)	-2.96 (1.73)	-0.54 (1.28)

Table 19. CUBAClinical BUA T-Scores and Z-Scores for Diagnostic Categories Defined by Spine BMD [Mean (SD)] for Study E

Diagnostic Class as Defined by Femoral Neck BMD T-Scores (# Subjects; %)	CUBAClinical BUA		Femoral Neck BMD	
	T-Score	Z-Score	T-Score	Z-Score
Normal (n=54;46%)	-1.13 (0.85)	-0.01 (0.85)	-0.60,(0.82)	-0.10 (0.95)
Osteopenic (n=40;34%)	-1.60 (0.70)	-0.42 (0.67)	-1.00 (0.87)	-0.63 (0.57)
Osteoporotic (n=24; 20%)	-2.18 (0.90)	-0.87 (0.82)	-1.78 (1.14)	-0.87 (0.97)

ROC curves were generated to evaluate the ability of the CUBAClinical to discriminate between osteoporotic and non-osteoporotic subjects as classified by femoral neck BMD and spine BMD T-Scores. The areas under the ROC curves with 95 percent confidence intervals are provided in Table 20. The highest AUC (0.85) was for CUBAClinical BUA.

Table 20. Areas under the ROC Curves for Discrimination of Osteoporotic from Non-Osteoporotic Subjects as defined by BMD (Femoral Neck and Spine) for Study E

Measurement Technique	Osteoporosis defined by BMD Femoral Neck T-Score AUC (95% CI)	Osteoporosis defined by BMD Spine T-Score AUC (95% CI)
CUBAClinical BUA	0.85 (0.69, 1.01)	0.74 (0.62, 0.86)
BMD Femoral Neck		0.72 (0.60, 0.84)
BMD Spine	0.78 (0.62, 0.94)	

Sensitivity and specificity for CUBAClinical BUA discrimination of osteoporotic subjects from non-osteoporotic subjects were determined for T-Score thresholds of -2.5, -2.0, and -1.5. Classification of each subject as osteoporotic was based on femoral neck or spine BMD T-Scores of -2.5 or less. Table 21 summarizes the sensitivity and specificity of BUA based on the resulting femoral neck or spine BMD classifications. It also shows the number of subjects that were classified as osteoporotic by both BUA and BMD. At a T-Score of -2.0, CUBAClinical BUA has a sensitivity of 64 percent, and a specificity of 78 percent when osteoporosis is defined by femoral neck BMD. Likewise, for a T-Score threshold of -2.0, when osteoporosis is defined by spine BMD, BUA has a sensitivity of 58 percent and a specificity of 82 percent.

Table 21. Summary of Sensitivity and Specificity for CUBAClinical BUA for Study E

CUBAClinical BUA T-Score Threshold		Femoral Neck BMD (n=11)	Spine BMD (n=24)
-2.5	Number of Subject (%)	6 (55%)	9 (38%)
	Sensitivity	55%	38%
	Specificity	92 %	94%
-2.0	Number (%) Identified	7 (64%)	14 (58%)
	Sensitivity	64%	58%
	Specificity	78%	82%
-1.5	Number (%) Identified	10 (91%)	16 (67%)
	Sensitivity	91%	67%
	Specificity	60%	61%

C. Precision

The precision of the CUBAClinical BUA has been reported in published clinical studies to be typically in the range of 2 to 4 percent. In 1996 Arden, et al., performed duplicate CUBAClinical BUA measurements on 30 subjects. Percent CV in these BUA measurements was 2.5 percent. These results were confirmed by Bennell, et al (1998) who performed three sequential measurements with repositioning between each measurement in each subject. Twenty normal, healthy subjects ranging in age from 25 to 56 years were enrolled in this study. The mean CV% was 2.96 percent for BUA. In 1997, Greenspan, et al. reported CV%

measurements of 4.3 to 4.4 percent in a study which measured instrument, positioning, short term and interobserver precision in four ultrasound devices. Interobserver precision was 7.58 percent in this study. The %CV for the other ultrasound devices in the study ranged from 2 percent to 9 percent. Njeh, et al., (1997) reported CV% of 4.3 percent for CUBAClinical BUA in thirty elderly patients. Each patient was measured twice during one visit. Five other bone sonometers were also included in the study and had CV% ranging from 1.9 percent to 6.4 percent for BUA. Pluijm, et al., (1999) recently reported results of a precision study in 20 healthy volunteers. CV% for the CUBAClinical BUA in these 20 subjects was 3.4 percent.

McCue, PLC also conducted an in vivo clinical precision study as part of the validation of the CUBAClinical 2.6. The purpose of the study was to compare the clinical precision of the CUBAClinical Mark 2.0 (the model used in the clinical studies) to the CUBAClinical Mark 2.6 (the model to be marketed in the U.S.). In this study precision of BUA and VOS, expressed as the percent coefficient of variation (CV%), was determined using two different operators who performed three separate measurements on fourteen subjects. The precision of the Mark 2.6 was found to be equal to, or better than, that of the Mark 2.0.

D. Reference Population

Three clinical sites, two in the United Kingdom and one in Ireland, provided the reference population data for the CUBAClinical software. Age dependent reference ranges for Caucasian females were developed for the CUBAClinical using BUA results for 4358 females from ages 20 through 80 who were evaluated at those clinical sites. The large number of subjects and geographic diversity minimizes the possibility of statistical or regional bias. The CUBAClinical uses the regression line and the pooled population standard deviation of the BUA measurements for this reference population for determining T-Scores and Z-Scores.

E. Comparability of Results Obtained in the Clinical Studies with those Obtained with the Proposed Product

To evaluate potential differences between the CUBAClinical Mark 2 used for the clinical studies presented in the PMA and the proposed CUBAClinical Mark 2.6, McCue PLC conducted a study of 55 subjects

who were enrolled at three different clinical sites. Measurements were performed by three different operators (one at each site) using the same Mark 2 and Mark 2.6 at all three sites. Results were analyzed using a Deming Regression.

Two regressions were run, one with the Mark 2 CUBAClinical BUA measurement as the dependent variable, and the other with the Mark 2.6 BUA measurement as the dependent variable. Estimates of the regression parameters are summarized in Table 22 below.

Table 22. Estimates of the Deming Regression Parameters

Dependent Variable	Estimate of Slope (SE)	95% CI for Slope	Estimate of Intercept (SE)	95% CI for Intercept
BUA (Mark 2/V3.6) Old	1.09 (0.011)	(1.071, 1.115)	-5.24 (0.798)	(-6.84, -3.64)
BUA (Mark 2.6/V4.1) New	0.92 (0.009)	(0.896, 0.934)	4.79 (0.682)	(3.43, 6.16)

It is important to note that the threshold between osteopenia and osteoporosis and therefore the area of greatest importance, is at CUBAClinical T-Scores between –1.5 and –2. These T-Scores coincide with BUA values of approximately 48 to 59 dB. As shown in the Deming regression, the two regression lines show the point of intersection (56.5, 56.5) to be in that region of interest. Thus, in the range of interest, differences between devices were minimal.

The results of the Deming regression analysis comparing the Mark 2 and proposed Mark 2.6 for this study therefore show that despite minor differences between the BUA measurements of the two devices, the clinical impact of these differences is negligible.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

A. Safety

There were no adverse effects from the McCue CUBAClinical measurements reported in any of the studies involving a total of 5775

subjects. This clinical experience, combined with the total worldwide experience with earlier versions of the CUBAClinical, demonstrates the safety of the CUBAClinical.

B. Effectiveness

The studies in the PMA show that the McCue CUBAClinical measures bone quality in subjects at risk for osteoporosis in a manner similar to bone mineral density (by ionizing radiation). CUBAClinical BUA measurements can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone density, and ultimately in the determination of fracture risk.

C. Risk/Benefit Analysis

The McCue CUBAClinical is safe and effective as a clinical indicator of skeletal status with performance comparable to that of bone mineral density measurements. Skeletal status and relative risk of fracture can be evaluated without the need for exposure to the ionizing radiation produced by the BMD devices. The acoustic output of the device is lower than the levels used by medical ultrasound imaging systems, which are considered safe. Based on the clinical and non-clinical evidence provided, the benefits of the CUBAClinical outweigh the risks of illness or injury when used according to the CUBAClinical User Manual.

XII. PANEL RECOMMENDATIONS N/A

XIII. FDA DECISION

The applicant's manufacturing facility was inspected on October 4-7, 1999 and was found to be in compliance with the device Good Manufacturing Practice regulations. FDA issued an approval order on January 7, 2000.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See attached labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520 (e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the attached labeling.

XV. REFERENCES

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LABELING

CUBACLINICAL

Incorporating

CUBA *plus+* software v4

USER MANUAL

- PLEASE READ THIS MANUAL THOROUGHLY -

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CONTENTS

1.0 Introduction and Background

The CUBAClinical is a patented 'dry' Ultrasonic Bone Sonometry System. By placing the calcaneus (heel bone) between two directly contacting Ultrasonic Transducers, rapid measurements of Broadband Ultrasonic Attenuation (BUA) are obtained. The calcaneus is a bone site of proven sensitivity to osteoporotic change.

This chapter provides an overview about ultrasound bone sonometry and the CUBAClinical. It includes a discussion of ultrasound measurement, safety precautions, system components and product specifications.

Essential prescribing information

Caution: Federal (U.S.A.) Law restricts this device to sale by or on the order of a physician.

1.1 Device Description

The CUBAClinical consists of the measurement unit, its power cord and computer connection cord, foot positioning inserts, and accessories. See section 'What is Supplied', below, for a complete list of accessories.

The CUBAClinical takes an ultrasound measurement through the patient's heel. The patient is seated with the foot accurately positioned into the footwell, using the correct positioning insert. The foot and lower part of the leg are secured using two Velcro® straps. Ultrasound gel is applied to the face of the silicone pads and to the sides of the heel to provide acoustic coupling. The silicone pads are brought into contact with each side of the patient's heel by means of a motorized mechanism. Inaudible sound waves are transmitted from one of the transducers through the heel and received by the other transducer. Quantitative parameters describing the attenuation in the heel are measured.

Patient examination time is short, with a typical measurement time of 1 minute (including a settling period).

1.2 Intended Use / Indications

The intended use of the CUBAClinical Ultrasonic Bone Sonometer is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid for the diagnosis of osteoporosis and other medical conditions leading to reduced bone density and ultimately in the determination of fracture risk.

The CUBAClinical measures two parameters, Broadband Ultrasound Attenuation (BUA in dB/MHz) which is used for the clinical measurement and Velocity of Sound (VOS, in m/s) which is used for QA purposes only. The BUA output is expressed both as an absolute value

and, with reference to the embedded Normative Data, as a T-Score, a Z-Score, and the percent expected (age-matched).

1.3 Contraindications

There are no contraindications.

1.4 Warnings

The CUBAClinical should not be used on subjects with breached skin (abraded skin) or open sores in any area of the lower leg, ankle, or foot that comes in contact with the System. Doing so may increase the risk of transmission of infection between patients.

The CUBAClinical requires proper cleaning and disinfecting procedures between each patient use. Doing so can help prevent transmission of infection between patients. Refer to Section 2.5 for cleaning and disinfection instructions.

Verify that the operating voltage specified on the rear panel of the System states 100 - 120 V AC, 50 - 60 Hz.

Any electrical outlet to which the CUBAClinical is connected **MUST** incorporate an effective earth (GROUND) connection.

Never use a damaged mains cable or allow loose connecting wires.

The CUBAClinical System is <u>not</u> designed for use in explosive or oxygen-enriched atmospheres.

All maintenance on the equipment must be performed by suitably qualified and trained personnel.

It is important for all users of the CUBAClinical to note and act upon all precautions and warnings in this and any other document concerned with this equipment particularly with reference to the following :

- The equipment must only be connected to the correct mains supply
- US models: are supplied with a "Hospital Grade" mains supply cord set meeting specification UL498. This type of cord set must be used. Grounding reliability can only be achieved when the equipment is connected, using the aforementioned cord set, to a receptacle labeled "Hospital Grade".
- After applying ultrasound gel to the patient and transducers, users should clean the gel from their hands before touching the equipment or computer.
- Hazardous voltages are present within the unit. The mains supply must be isolated before any maintenance work is performed or the enclosure removed.
- The use of components, modules or any modifications not approved by McCue will invalidate the warranty on the product.

The CUBAClinical is **NOT designed to be USER serviceable**. Other than for external cleaning, no regular maintenance is required.

Removal of the outer case and any unauthorized adjustment to the electronics within will result in the need for the System to be recalibrated by an authorized service agent.

Contact your authorized service agent for repairs. Unauthorized repairs or modifications will VOID all warranties.

1.5 Precautions

- The CUBAClinical is not protected against the ingress of liquids and should be used only in a clean, dry environment.
- Do not store the CUBAClinical near to a heat source, window or air conditioner.
- Only the CUBAClinical QA Phantom should be used to verify the calibration of the CUBAClinical System.
- The QA Phantom should be stored close to the CUBAClinical and under the same conditions.
- Never leave the QA Phantom in the CUBAClinical footwell with the transducers in the closed position.
- CUBAClinical ultrasound gel is for external use only.
- Interfacing equipment (Computer, printer) used with the CUBAClinical must meet IEC 950, or equivalent safety standards.
- Animal studies of the material used for the CUBAClinical case and external parts (acrylic-coated ABS plastic) suggest that this material may be a potential sensitizer.

1.6 Adverse Events

There are no known potentially adverse effects from the CUBAClinical on health. Since the launch of the CUBAClinical in June 1992 over 500 Systems have been sold world-wide (except North America) and many tens of thousands of measurements have been performed. No adverse events of any kind have been reported.

1.7 Clinical Studies

Five studies performed at six sites in the United States and Europe were conducted to assess the safety, effectiveness, and clinical utility of the McCue CUBAClinical. Study A evaluated the CUBAClinical and four other calcaneal bone assessment instruments for precision, correlation, and discrimination ability. Study B was conducted to determine the possible contribution of CUBAClinical BUA for assessing risk of osteoporotic fracture in the elderly. Results for Studies A and B are described here. Results of three additional studies conducted at two sites in the United Kingdom which demonstrate the diagnostic performance of the CUBAClinical and how it compares with DEXA BMD are provided in Appendix 1 to this Manual.

STUDY A: Fosamax Protocol 349

This study was conducted at two clinical sites in the United States to determine if measuring skeletal status at the calcaneus is a useful technique for diagnosis of osteoporosis and evaluated the CUBAClinical and four other calcaneal bone assessment instruments for precision, correlation, and discrimination ability. The study enrolled a total of 161 Caucasian women: 53 were "young normal" women between the ages of 20 and 35 (mean age: 30.2); and 52 were osteoporotic women with no history of fracture; and 56 were osteoporotic women without a history of fracture. The 108 osteoporotic women were all between the age of 55 and 92 (mean age: 72.5). Subjects were considered to be osteoporotic if they had a femoral neck or trochanter BMD T-score of -2.5 or lower. CUBAClinical BUA measurements were performed on the subjects using the CUBAClinical as well as DEXA and SEXA of the calcaneus, hip, and spine. In addition, measurements were performed using three other calcaneal ultrasound devices, but these devices were not included in the analysis presented in the PMA. Complete results for all devices tested are provided in a report published by Greenspan, et al (1997).

Femoral neck and trochanter BMD T-Scores using device-specific reference populations were used to qualify subjects for enrollment in the osteoporotic cohorts. T-Scores for all instruments for all other analyses were determined using the young normal subjects, thereby providing a common reference population.

Pearson's product moment correlation coefficients were determined for age and CUBAClinical BUA measurements and for the DEXA and SEXA devices. For all study subjects, the correlation between subject age and the instrument measurements ranged from -0.677 (BMD calcaneus) to -0.836 (BMD femoral neck). The correlation coefficient for CUBAClinical BUA was approximately in the middle of this range at -0.743.

The correlation of the CUBAClinical BUA T-scores to the T-scores for the BMD measurements were determined. Pearson's correlation coefficients for BUA versus each of the DEXA and SEXA devices ranged from 0.696 (BUA versus DEXA of the trochanter) to 0.821 (BUA versus DEXA of the calcaneus). Correlations among the different BMD measurements ranged from 0.729 (DEXA calcaneus versus DEXA femoral neck) to 0.908 (DEXA calcaneus versus SEXA calcaneus).

T-scores for fracture and non-fracture cohorts are given in Table 1 for CUBAClinical BUA measurements, DEXA measurements, and SEXA measurements at different anatomical sites. For all of the devices studied, the mean T-scores for the fracture groups were significantly lower than the mean T-scores for the non-fracture groups ($p<.02$). Duncan's Multiple Range Test was used to compare the mean T-scores for the CUBAClinical BUA and the SEXA and DEXA measurements for all osteoporotic subjects. This test found that the mean T-score for CUBAClinical BUA was not significantly different from the mean BMD T-scores for DEXA calcaneus and DEXA trochanter. BMD T-scores for DEXA femoral neck and SEXA calcaneus were also not significantly different.

Table 1. Summary of T-Scores for Study A Osteoporotic Subjects

Instrument		Osteoporotic		
		No Fracture (n=49)	Fracture (n=55)	All (n=104)
CUBAClinical BUA	Mean	-1.77	-2.24	-2.02
	SD	0.837	0.859	0.877
OsteoAnalyzer (BMC)	Mean	-1.99	-2.62	-2.32
(SEXA calcaneus)	SD	1.015	1.186	1.148
QDR-1500/2000 (BMD)	Mean	-1.76	-2.305	-2.05
(DEXA calcaneus)	SD	1.141	1.219	1.208
QDR-1500/2000 (BMD)	Mean	-1.71	-2.13	-1.93
(DEXA trochanter)	SD	0.698	0.810	0.783
QDR-1500/2000 (BMD)	Mean	-2.30	-2.54	-2.43
(DEXA femoral neck)	SD	0.413	0.592	0.527

The ability of CUBAClinical BUA, DEXA calcaneus BMD, and SEXA calcaneus BMD to discriminate between osteoporotic and non-osteoporotic controls was assessed for T-score thresholds of -2.5 and -2.0. For a T-score threshold of -2.5, the proportion of subjects classified as osteoporotic by CUBAClinical BUA was 31 percent. This compares to 39 percent and 47 percent for DEXA calcaneus and SEXA calcaneus, respectively. For a T-score threshold of -2.0, the number of subjects correctly classified as osteoporotic ranged from 53 to 69 percent, with CUBAClinical BUA at 58 percent.

Receiver-Operator Characteristic (ROC) curves were generated to determine the ability of CUBAClinical BUA and DEXA and SEXA of the calcaneus to discriminate osteoporotic subjects from the young normal control group. In addition, ROCs and the areas under the ROC curves were generated to discriminate between osteoporotic subjects with fractures from those without fractures. The area under an ROC curve provides a figure of merit for comparing one curve to another. The AUC must be greater than 0.5 if the diagnostic ability is better than chance. A summary of the AUCs obtained for the three instruments is provided in Table 2.

Table 2. Areas Under the ROC Curves for Study A

Instrument	Control vs Osteoporotic AUC (95%CI)	Osteoporotic w/o vs Osteoporotic w/fracture AUC (95%CI)
CUBAClinical BUA	0.93 (0.89, 0.97)	0.63 (0.53, 0.73)
OsteoAnalyzer (SEXA calcaneus)	0.93 (0.89, 0.97)	0.65 (0.55, 0.75)
QDR 1500/2000 (DEXA calcaneus)	0.90 (0.86, 0.94)	0.62 (0.52, 0.72)
QDR 1500/2000 (DEXA trochanter)	0.93 (0.89, 0.97)	0.65 (0.52, 0.75)
QDR 1500/2000 (DEXA femoral neck)	0.98 (0.96, 1.00)	0.60 (0.48, 0.72)

To further compare the discriminatory ability of CUBAClinical BUA to the X-ray absorptiometry instruments, the sensitivity and specificity of each instrument was determined for T-score thresholds of -1.5, -2.0, and -2.5. The results, summarized in Table 3, indicate that the sensitivity and specificity of CUBAClinical BUA is comparable to that of SEXA of the calcaneus and DEXA of the calcaneus.

Table 3. Comparison of Sensitivity and Specificity of Calcaneal Instruments in Study A

Instrument	T-Score Threshold	Sensitivity (%)	Specificity (%)
CUBAClinical BUA	-1.5	77	96
	-2.0	58	96
	-2.5	31	100
QDR-1500/2000 (DEXA calcaneus)	-1.5	69	92
	-2.0	54	98
	-2.5	36	98
OsteoAnalyzer (SEXA calcaneus)	-1.5	77	94
	-2.0	67	96
	-2.5	44	100

STUDY B: Netherlands Study of Fracture Risk

This prospective longitudinal study was conducted to determine the possible contribution of CUBAClinical BUA for assessing risk of osteoporotic fracture in the elderly. The study was conducted at the Institute of Research in Extramural Medicine, Academic Hospital, Vrije University, Amsterdam, The Netherlands. Dr. S.M.F. Pluijm was the Principle Investigator. A total of 710 Caucasian subjects between the ages of 70 and 99 were enrolled in the study, of whom 578 were women and 132 were men. Subjects were excluded if they were unable to give informed consent, had a history of calcaneal fracture, were confined to bed, or used a wheelchair.

CUBAClinical measurements were performed at time of enrollment. Subjects were contacted every six months by telephone or self-administered mail questionnaire to determine if they had a fall or fracture during the previous month. Fractures were verified with the subject's primary physician. During the time of the study, 168 subjects died and 5 were lost to follow-up. The study accumulated 1844 person-years of follow-up (median: 2.8 years, maximum: 3.7 years).

During the period of follow-up, 77 of the subjects (73 females and 4 males) sustained a total of 96 fractures (31 hip and 65 other non-spinal fractures). Table 4 compares the baseline CUBAClinical BUA measurement for the 77 subjects with fractures and the subjects without fractures. The differences in BUA between the fracture and non-fracture groups were statistically significant for both men and women.

Table 4. Summary of Baseline CUBAClinical BUA Measurements by Fracture Status and Sex for Study B

	CUBAClinical BUA (dB/MHz) (Mean (SD))		
	Fracture	Non Fracture	p value*
Female Mean (SD)	n=73 51.27 (15.88)	n=503 56.92 (17.52)	0.010
Male Mean (SD)	n=4 66.81 (16.56)	n=128 81.05 (21.57)	0.194
Combined Mean (SD)	n=77 52.08 (16.18)	n=631 61.81 (20.80)	<0.001

Significance level for paired t-test comparing mean for fracture versus non-fracture subjects.

Relative hazard ratios were determined using Cox proportional hazard regression and are reported here with 95 percent confidence intervals. The relative hazard ratio of hip fracture, other non-spinal fracture, and any non-spinal fracture for one standard deviation decrease in CUBAClinical BUA is summarized by subject sex and for all subjects in Table 5. An increased relative hazard ratio is indicated by a relative risk of greater than 1.0. As shown in Table 5, the relative hazard ratio for CUBAClinical BUA is greater than 1.0 for hip fractures and any fracture in female subjects. The lower 95 percent confidence interval is less than 1.0 for other non-spinal fractures, and for all fracture endpoints in the male population.

Table 5. Relative Risk of Hip, Other Non-Spinal, and Any Non-Spinal Fracture for CUBAClinical BUA for Study B

Gender		Hip Fracture		Other Non-Spinal Fractures		Any Non-Spinal Fracture	
		RR	95%CI	RR	95%CI	RR	95%CI
Females	BUA	2.27	1.41-3.66	1.29	0.96 - 1.73	1.52	1.17 - 1.97
Males	BUA	2.68	0.79 - 9.06	2.71	0.24 - 30.71	2.68	0.79 - 9.06
Overall	BUA	2.34	1.46 - 3.75	1.62	1.18 - 2.22	1.83	1.39 - 2.42

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1.8 Individualization of treatment

The CUBAClinical measures BUA of the heel. These results are used by the physician to assess skeletal status in the evaluation of patients at risk of osteoporosis and other metabolic bone conditions and / or patients who may have reduced bone density due to medical conditions indirectly affecting bone mineral metabolism, medications prescribed for other conditions, heritable or genetic factors, lifestyle factors, or other reasons. BUA may be used by the physician along with other clinical factors in the diagnosis of osteoporosis and other conditions leading to reduced bone density.

When evaluating individual patients, all relevant risk factors should be considered. (Previous fractures, frame size, smoking, age etc.)

1.9 Patient counseling information

A Patient Information Package is available from your CUBAClinical supplier. This booklet provides an introduction to the condition of osteoporosis, the cause, treatment, and prevention and also explains the CUBAClinical measurement and report.

1.10 Conformance to Standard

There are no known adverse effects of this device on health. The ultrasound power levels used by the CUBAClinical are lower than standard imaging ultrasound devices which are widely used and accepted.

1.11 What is Supplied

The CUBAClinical shipping package includes the following :

- One CUBAClinical Unit
- One Padded carrying bag for the CUBAClinical unit
- One Serial Cable
- One Power Cable (the type supplied will be appropriate to the country of destination)
- One User's Manual
- One QA Phantom
- One Padded carrying bag for the Phantom
- CUBA plus+ V4 software installation disk/s
- One bottle of ultrasound gel
- Two inserts (for correctly positioning the patient's foot)

1.12 Quantitative Ultrasound (QUS) as a Tool for the Assessment of Bone Status

In the medical field, ultrasound is commonly used to obtain 2-dimensional soft tissue images. However, it may also be used to characterize the physical properties of cancellous (trabecular) bone.

Quantitative Ultrasound (QUS) possess advantages over the traditional techniques (radiographs, x-ray absorptiometry, computed tomography) for assessment of bone mass. QUS is quick, non-ionizing and low cost and it provides information relating to characteristics of bone (structure, elasticity) in addition to density, that are important in the determination of fracture risk.

Cancellous bone is eight times more metabolically active than cortical bone and age and disease related bone loss are more readily apparent at sites where there is a high percentage of this type of bone. The calcaneus (heel) is a bone that is 75 – 90% cancellous. There is little soft tissue surrounding the bone making it an excellent site for QUS measurement and hence the determination of a patients risk of fracture.

QUS measurements obtained using the CUBAClinical are compared to a normative database and expressed in terms of "T" score, "Z" score, and % expected (age matched). The T-Score and Z-Score values are also displayed graphically for quick and easy interpretation.

1.13 What the CUBAClinical Measures

The CUBAClinical measures two parameters, BUA (Broadband Ultrasound Attenuation) for clinical measurements and additionally VOS (Velocity of Sound) which is used in the QA test.

The more complex the structure of the bone, the more the sound wave will be blocked. Therefore, normal bone has a higher attenuation (BUA) than osteoporotic bone. Likewise the greater the connectivity of tissue, the faster the sound wave will pass through it. As bone becomes osteoporotic the architecture diminishes and the speed of the sound wave slows down.

BUA is compared to results obtained from a normative population and expressed graphically and in the following terms by % expected for the subjects age group, Z-Score, and T-Score.

1.14 CUBAClinical System Overview

The CUBAClinical is a portable ultrasound device that measures BUA of the calcaneus. These data are compared to a reference value in order to assess the bone status of the patient relative to race, age and gender. Reference values for Caucasian women are supplied with the System.

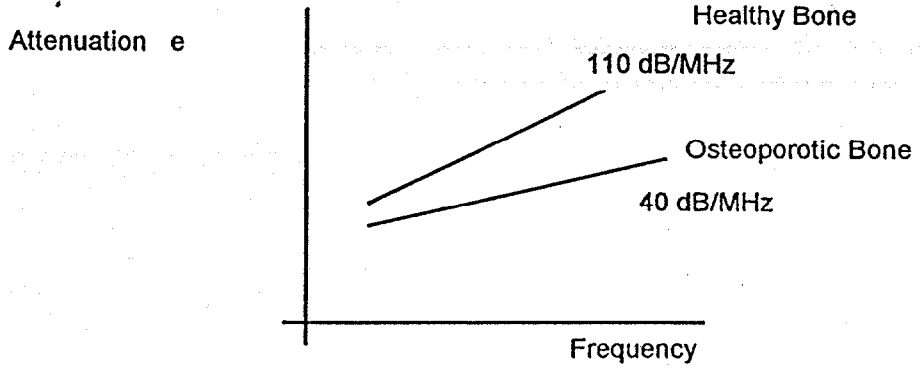
The measurement is taken with the patient seated. Their foot is positioned by use of an anatomical insert (based on foot length) and the foot and leg are secured by the use of two straps. The transducers are brought into contact with each side of the calcaneus, and acoustic coupling is achieved by the use of silicone pads and ultrasound gel. The silicone pads are permanently attached to the transducers and the ultrasound gel is applied prior to each patient measurement. A sound wave is passed through the heel taking only a few minutes to provide the patient with an indication of their fracture risk status.

The patient will be unaware of the measurement process as the sound waves produced by the CUBAClinical are outside the range of human tissue sensation.

1.15 Ultrasound Measurement Using the CUBAClinical

A high frequency (non audible) sound wave is passed from one transducer (the transmitter) through the heel to another transducer (the receiver). Acoustic coupling is achieved by the use of silicone pads and ultrasound gel. The parameter measured by the receive transducer is the attenuation of the received signal (BUA).

Broadband Ultrasound Attenuation



The attenuation of ultrasound (dB) at a particular frequency (MHz) is defined as the ratio of signal amplitude (volts) for a reference material and the measured bone. There is a linear relationship between attenuation and frequency for cancellous bone between 0.2 MHz and 0.6 MHz to which a regression is applied, yielding the BUA index of units dB/MHz-1. The reference trace (a measurement through de-gassed water) is performed in the factory and stored within the CUBAClinical. The range of BUA observed with the CUBAClinical in a typical population is approximately 23 to 124 dB/MHz with young healthy subjects having a higher BUA than older osteoporotic subjects.

1.16 Relationship between CUBAClinical Results and Risk of Fracture

Prospective clinical studies have demonstrated that subjects with low BMD are at higher risk of fracture. The risk of fracture increases exponentially with decreasing BMD. For example, for Hip fracture, it has been demonstrated that with a 1 SD decrease in hip BMD there is a two to three fold increase in the risk of hip fracture. (A two fold increase is often reported as a relative risk of 2).

It has also been demonstrated that a similar relationship exists between heel ultrasound and hip fracture with approximately a two fold increase in the risk of fracture per 1 standard deviation (SD) decrease in BUA.

A recent prospective study using the CUBAClinical confirmed previous findings. A decrease of one SD in BUA was associated with more than a two-fold increase (2.3 RR) in hip fracture and a 60% (RR 1.6) increase in the risk of any fracture.

In summary, prospective studies have demonstrated the strong exponential relationship between heel ultrasound and x-ray results, and the ability of the CUBAClinical to predict the risk of future fracture.